Amendments to the Specification:

Please replace the paragraph beginning at page 1, line 7, with the following amended paragraph:

The present application is a continuation of Application No. 09/311,772, filed May 13, 1999, which is a continuation of Application No. 09/024,932, filed February 17, 1998, which claims priority from ~~claims priority from USSN 08/801,285, filed February 18, 1997; USSN. 08/801,681, filed February 18, 1997; USSN 08/801,755, filed February 18, 1997; USSN 08/801,765, filed February 18, 1997~~ U.S. Provisional Application No. 60/038,065, filed February 18, 1997, now abandoned; and, U.S. Provisional Application No. 60/047,834, filed May 28, 1997, now abandoned. Each of the aforementioned applications is explicitly incorporated herein by reference in their entirety and for all purposes.

Please replace the paragraph beginning at page 2, line 6, with the following amended paragraph:

Of the many available chemotherapeutic drugs, paclitaxel, available commercially as [[Taxol]] TAXOL® (NSC number: 125973) has generated interest because of its efficacy in clinical trials against drug-refractory tumors, including ovarian and mammary gland tumors (Hawkins (1992) *Oncology*, 6: 17-23, Horwitz (1992) *Trends Pharmacol. Sci.* 13: 134-146, Rowinsky (1990) *J. Natl. Canc. Inst.* 82: 1247-1259). Recent studies on the interaction of paclitaxel and tumor suppressor gene therapy show that reduced levels of tumor suppressor (*i.e.*, p53) correlated with increased G2/M phase arrest, micronucleation, and p53 independent paclitaxel-induced apoptosis. In contrast, surviving cells with intact p53 progressed through mitosis and transiently accumulated in the subsequent G1 phase, coincident with increased p53 and $p21^{cip1,waf1}$ protein levels (Wahl (1996) *Nature Med.* 2:72-79). Similarly, Hawkins (1996) *Canc. Res.* 56: 892-898, showed that inactivation of p53 enhanced sensitivity to certain antimitotic agents including paclitaxel. The authors suggested that p53 may play a role in DNA repair, thereby allowing cells to progress more readily through S phase even in the presence of drugs. These studies thus suggest that tumor suppressor gene therapy and drug therapy with anti-mitotic agents (especially paclitaxel therapy) act at cross purposes.

Please replace the paragraph beginning at page 4, line 11, with the following amended paragraph:

Preferred paclitaxel or paclitaxel derivatives include paclitaxel (sold under the trademark TAXOL®) and/or ~~Taxolere®~~ TAXOLERE® (docetaxel) with paclitaxel (~~Taxol®~~ TAXOL®) being most preferred. Another preferred adjunctive anti-cancer is Epothilone. In one particularly preferred embodiment, the tumor suppressor is A/C/N/53 and the adjunctive anti-cancer agent is paclitaxel.

Please replace the paragraph beginning at page 13, line 27, with the following amended paragraph:

The term "paclitaxel" as used herein refers to the drug commercially known as [[Taxol]] TAXOL®. [[Taxol]] TAXOL® inhibits eukaryotic cell replication by enhancing polymerization of tubulin moieties into stabilized microtubule bundles that are unable to reorganize into the proper structures for mitosis.

Please replace the paragraph beginning at page 15, line 10, with the following amended paragraph:

Figure 1 illustrates the *in vitro* inhibition of SK-OV-3 ovarian tumor cells by various concentrations of p53 (A/C/N/53) and/or [[Taxol]] TAXOL®.

Please replace the paragraph beginning at page 15, line 12, with the following amended paragraph:

Figure 2 provides an isobologram analysis for the experiments illustrated in Figure 1. Synergism between [[Taxol]] TAXOL® and p53 (A/C/N/53) was observed when the cells were pretreated with [[Taxol]] TAXOL® 24 hours before p53 treatment.

Please replace the paragraph beginning at page 16, line 24 (spanning pages 16 and 17), with the following amended paragraph:

It was a surprising discovery of this invention that, contrary to the results described in previous studies (*see, e.g.*, Wahl *et al.* (1996) *Nature Med.*, 2(1): 72-79, and Hawkins *et al.* (1996) *Canc. Res.* 56: 892-898), the treatment of mammalian cells lacking or deficient in endogenous wild-type tumor suppressor protein (*i.e.*, many neoplastic cells), with both an adjunctive anti-cancer agent (*e.g.*, paclitaxel ([[Taxol]] TAXOL®)) and a tumor suppressor gene or polypeptide (*e.g.*, p53) results in inhibition of proliferation and/or growth of the cells greater than that observed with either the chemical treatment or the tumor suppressor construct alone. Moreover, it was a discovery of this invention that pretreatment with adjunctive anti-cancer agents dramatically increases the anti-proliferative effect of a tumor suppressor nucleic acid. Without being bound by a particular theory, it is believed that possible means by which an adjunctive anti-cancer agent may contribute to this enhanced effect is: to increase the transfection efficiency of various gene therapy vectors (*e.g.*, adenovirus vectors); or, to increase expression levels of the tumor suppressor gene; or, to stabilize microtubules to assist in intracellular virus transport; or, to provide enhanced effect through the interaction of various intracellular mechanisms (*e.g.*, signaling pathways, apoptotic pathways, cell cycling pathways).

Please replace the paragraph beginning at page 19, line 15, with the following amended paragraph:

Microtubule affecting agents useful in the invention are well known to those of skill in the art and include, but are not limited to allocolchicine (NSC 406042), Halichondrin B (NSC 609395), colchicine_(NSC 757), colchicine derivatives (e.g., NSC 33410), dolastatin 10 (NSC 376128), maytansine_(NSC 153858), rhizoxin (NSC 332598), paclitaxel ([[Taxol]] TAXOL®, NSC 125973), [[Taxol]] TAXOL® derivatives (e.g., NSC 608832), thiocolchicine (NSC 361792), trityl cysteine (NSC 83265), vinblastine sulfate (NSC 49842), vincristine sulfate (NSC 67574), epothilone A, epothilone, and discodermolide (*see* Service, (1996) *Science*, 274: 2009) estramustine, nocodazole, MAP4, and the like. [[ ]]Examples of such agents are also described in the scientific and patent literature, see, *e.g.*, Bulinski (1997) *J. Cell Sci.* 110:3055-3064; Panda (1997) *Proc. Natl. Acad. Sci.* USA 94:10560-10564; Muhlradt (1997) *Cancer Res.* 57:3344-3346; Nicolaou (1997) *Nature*

387:268-272; Vasquez (1997) *Mol. Biol. Cell.* 8:973-985; Panda (1996) *J. Biol. Chem.* 271:29807-29812.

Please replace the paragraph beginning at page 26, line 26 (spanning pages 26 and 27), with the following amended paragraph:

Dosages for typical chemotherapeutics are well known to those of skill in the art. Moreover, such dosages are typically advisorial in nature and may be adjusted depending on the particular therapeutic context, patient tolerance, etc. Thus, for example, a typical pharmaceutical composition (I, paclitaxel) dosage for intravenous (IV) administration would be about 135 mg/m^2 administered over 1-24 hours (typically at 1, 3, or 6 hours, more preferably 3 hours) and more preferably repeated every three weeks for 3 to 6 cycles. To decrease the frequency and severity of hypersensitivity reactions, patients may also receive about 20 mg of dexamethasone (Decadron, and others) orally about 12 hours and 6 hours before, and about 50 mg of diphenhydramine (~~*Benadryl*~~ BENADRYL®, and others) plus about 300 mg of cimetidine (~~*Tagamet*~~ TAGAMET®) or 50 mg of rantidine (~~*Zantac*~~ ZANTAC®) IV 30 to 60 minutes before treatment with paclitaxel. Considerably higher dosages (*e.g.*, ranging up to up to about 350 mg/m^2 per day may be used, particularly when the drug is administered to a secluded site and not into the blood stream, such as into a body cavity or into a lumen of an organ. Substantially higher dosages are possible by any selected route, for example, topical administration. Actual methods for preparing parenterally administrable compositions will be known or apparent to those skilled in the art and are described in more detail in such publications as Remington's Pharmaceutical Science, 15th ed., Mack Publishing Company, Easton, Pennsylvania (1980) and U.S. Patent Nos: 5,583,153, 5,565,478, 5,496,804, and 5,484,809. Typical doses, *e.g.*, for intraperitoneal administration, will be 20-150 mg/m^2 weekly, or about 250 mg/m^2 every 3 weeks.

Please replace the paragraph beginning at page 53, line 19, with the following amended paragraph:

The pretreatment is particularly efficacious when the adjunctive anti-cancer agent is a paclitaxel-like compound, more preferably paclitaxel or a paclitaxel derivative

(*e.g.*, [[Taxol]] TAXOL® or ~~Taxolere~~ TAXOTERE®). Particularly preferred tumor suppressors are RB and p53 with p53 being most preferred, in particular p53 in an adenoviral vector (*e.g.*, A/C/N/53).

Please replace the paragraph beginning at page 55, line 16, with the following amended paragraph:

Exemplary ointment carriers include petroleum based ~~Puralube~~ PURALUBE® or water soluble ~~KJ Jelly~~ KY-JELLY®. In an exemplary method, sterile gauze pads (5 x 5 cm) or tear flow test strips can be soaked in an adenoviral vector solution (*e.g.*, 1 x 10^9 PN/ml) until totally wet. The pads or strips are layered on top of the target tissue and incubated at 37 degrees C for 30 minutes. One of skill will recognize that other fabrics, gelatins, or ointments can be included that can take up or be mixable with water. In addition, other excipients may be added that can enhance gene transfer as described above.

Please replace the paragraph beginning at page 61, line 2, with the following amended paragraph:

Combination Therapy with p53 and [[Taxol]] TAXOL®

The invention provides for the combined administration of nucleic acid expressing a tumor suppressor polypeptide and paclitaxel in the treatment of neoplasms. [[ ]]The following example details the ability of a p53 expressing adenovirus of the invention in combination with [[Taxol]] TAXOL® to treat neoplasms, and that the combination therapy was more effective at killing tumor cells than either agent alone.

Please replace the paragraph beginning at page 61, line 9, with the following amended paragraph:

The cells were subjected to one of three treatment regimes: In treatment 1, the cells were pretreated with [[Taxol]] TAXOL® twenty-four hours before exposure to the p53 adenovirus construct A/C/N/53. In treatment two, the cells were pretreated with the p53 adenovirus construct and then later contacted with [[Taxol]] TAXOL®. In treatment three, the cells were contacted simultaneously with both the [[Taxol]] TAXOL® and the p53

adenovirus. Thus, the p53 Ad and [[Taxol]] TAXOL® can be administered within the same twenty four (24) hour period or concurrently.

Please replace the paragraph beginning at page 61, line 16, with the following amended paragraph:

Approximately 1.5 x 10^4 cells in culture medium (head and neck cell lines SCC-9, SCC-15, and SCC-25 in 1:1 mix of DMEM + Ham's F12 media with 0;4 μg/ml cortisol and 10% FBS and 1% non-essential amino acids, prostate DU-145 and Ovarian SK-OV-3 in Eagles essential medium plus 10% FBS) were added to each well on a 96 well microtitre plate and cultured for about 4 hours at 37°C and 5% CO_2. The drug ([[Taxol]] TAXOL®), the p53 adenovirus, or the appropriate vehicle/buffer was added to each well. As paclitaxel is not water soluble, the drug was dissolved in ethyl alcohol prior to administration. Cells were then cultured overnight at 37°C and 5% CO_2. p53 adenoviruses were administered in phosphate buffer (20 mM NaH_2PO_4, pH 8.0, 130 mM NaCl, 2 mM $MgCl_2$, 2% sucrose).

Please replace the paragraph beginning at page 62, line 3, with the following amended paragraph:

Table 1. In vitro evaluation of the adjunctive anti-cancer agent [[Taxol]] TAXOL® combined with tumor suppressor nucleic acid.

Cell line Cancer	[[Taxol]] TAXOL® dose (μg/ml)	A/C/N/53 dose (m.o.i.)	Treatment		
			[[Taxol]] TAXOL® pretreatment	p53 pretreatment	simultaneous
SK-OV-3 Ovarian cancer	0.37	40	additive effect $p \leq 0.0001$	no effect $p > 0.2000$	additive effect $p \leq 0.0001$
SCC-25 Head and neck cancer	0.10 or 0.01	2.5 or 5.0	additive effect $p \leq 0.0001$	very small effect $p = 0.0606$	additive effect $p \leq 0.0001$
SCC-15 Head and neck cancer	0.10 or 0.01	2.5 or 5.0	additive effect $p \leq 0.002$	additive effect $p \leq 0.0001$	additive effect $p \leq 0.0001$
DU-145 Prostate cancer	0.36 or 0.036 or 0.0036	2.5 or 5.0	additive effect $p \leq 0.03$	additive effect $p \leq 0.0001$	additive effect $p \leq 0.0001$
SCC-9 Head and neck cancer	0.12 or 0.012 or 0.0012	2.5 or 5.0	additive effect $p \leq 0.01$	additive effect $p \leq 0.0001$	additive effect $p \leq 0.0001$

Please replace the paragraph beginning at page 62, line 27, with the following amended paragraph:

In general, the p53 adenovirus was more effective when added after or concurrently with [[Taxol]] TAXOL® than when it was added first. These results suggest a synergistic interaction between A/C/N/53 and [[Taxol]] TAXOL®.

Please replace the paragraph beginning at page 62, line 31 (spanning pages 62 and 63), with the following amended paragraph:

SK-OV-3 (p53 null) ovarian tumor cells were treated with combinations of [[Taxol]] TAXOL® and p53/adenovirus (A/C/N/53) as illustrated in Table 2. Dosing was performed as described above. Cell death was quantitated on day 3 using the MTT assay as described above. In addition, a dose response curve for p53 Ad alone (using the doses listed in Table 2) was generated (after 2 day cell exposure to the drug) and a dose response curve for [[Taxol]] TAXOL® alone was performed using the doses listed above (3 day cell exposure to the drug).

Please replace the paragraph beginning at page 62 (table 2), line 4 (spanning pages 63 and 54), with the following amended paragraph:

Table 2. Treatment groups for combined [[Taxol]] TAXOL® and p53 Ad (A/C/N/53) treatments.

Group	[[Taxol]] TAXOL® (μg/ml)	p53 AD (m.o.i.)	Group	[[Taxol]]TAXOL® (μg/ml)	p53 AD (m.o.i.)
1	0.001	0.5	25	0.001	10
2	0.01	0.5	26	0.01	10
3	0.1	0.5	27	0.1	10
4	0.5	0.5	28	0.5	10
5	1	0.5	29	1	10
6	5	0.5	30	5	10
7	10	0.5	31	10	10
8	20	0.5	32	20	10
9	0.001	1	33	0.001	25

10	0.01	1	34	0.01	25
11	0.1	1	35	0.1	25
12	0.5	1	36	0.5	25
13	1	1	37	1	25
14	5	1	38	5	25
15	10	1	39	10	25
16	20	1	40	20	25
17	0.001	5	41	0.001	50
18	0.01	5	42	0.01	50
19	0.1	5	43	0.1	50
20	0.5	5	44	0.5	50
21	1	5	45	1	50
22	5	5	46	5	50
23	10	5	47	10	50
24	20	5	48	20	50

Please replace the paragraph beginning at page 64, line 2, with the following amended paragraph:

Figure 1 illustrates the inhibition of cell proliferation (as compared to the buffer control) as a function of treatment. In general increasing doses of either [[Taxol]] TAXOL® or p53 decreased the rate of cell proliferation with the combination of p53 and [[Taxol]] TAXOL® having a greater effect than either drug alone.

Please replace the paragraph beginning at page 64, line 7, with the following amended paragraph:

Figure 2 illustrates an isobologram analysis of these data using the Isobole method as reviewed by Berenbaum (1989) *Pharmacol. Rev.* 93-141. Synergism between [[Taxol]] TAXOL® and p53 (A/C/N/53) was observed when cells were pretreated with [[Taxol]] TAXOL® 24 hours before p53 (A/C/N/53) treatment. In Figure 2, the straight line (isobole for ED_{30}) represents the effects on cell proliferation which would be expected if treatment with the two drugs were merely additive. In fact, the observed effects fall to the lower left of the isobole line indicating that lower than predicted concentrations of each drug were needed and a synergistic interaction between the two drugs has occurred.